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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,279	KLOCK ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-10 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13* is/are allowed.

6)☒ Claim(s) *1,8-10 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 19 May 2009.

Claim Status

Claims 1, 8-10 and 13-20 are pending. Claims 2-7 and 11-12 are cancelled. Claims 1, 8, 13, 17, 18 and 19 are amended. Claims 1, 8-10 and 13-20 are under examination.

Priority

This application claims benefit from as a 371 of PCT/EP04/14097 (filed 12/10/2004). In addition, the application claims benefit from foreign application GERMANY DE 103 58 407.2 (filed 12/11/2003). The instant application has been granted the benefit date, 10 December 2004, from the application PCT/EP04/14097.

RESPONSE TO ARGUMENTS

35 USC § 112, 2nd

The rejection of claims 11-12 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicants claim amendments. The applicant's claim amendments have been fully considered and are persuasive. The applicant has cancelled claims 11-12. Therefore, the rejection is moot. Therefore, the examiner hereby withdraws the rejection of claims 11-12 under 35 USC 112, 2nd paragraph.

35 USC § 112, 1st (enablement)

The rejection of claims 11-12 under 35 USC 112, 1st paragraph is withdrawn in response to the applicants claim amendments. The applicant's claim amendments have been fully considered and are persuasive. The applicant has cancelled claims 11-12. Therefore, the rejection is moot. Therefore, the examiner hereby withdraws the rejection of claims 11-12 under 35 USC 112, 1st paragraph.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claim 13 under 35 U.S.C. 102(b) as being anticipated by Morris (WO2003/039484, published 15 May 2003) is withdrawn in response to the applicant's claim amendments. However, claims 18-20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Morris (WO2003/039484, published 15 May 2003) for the reasons of record and the comments below.

The applicant's arguments and claim amendments have been fully considered and are partially persuasive. The applicant has amended the claim 13 so that scope of

the instant claims cannot be interpreted as merely a dinucleotide. Therefore, instant claim 13 is not anticipated by Morris.

However, although claims 18-20 have been amended, the scope of these claims can still be interpreted as being anticipated by the sequences of Morris. The examiner apologizes to the applicant for seeming to contradict himself. In the previous action, the examiner indicated that if amended as instructed (1/23/2009, page 12), the claim language of claims 18-20 would be satisfactory to overcome the pending 35 USC 102 rejection. However, after discussion with the examiner's supervisor, the examiner was instructed to maintain the pending rejection. The examiner has included a copy of the TC1600 memo regarding interpreting claim language directed to sequences having SEQ ID NOs. The examiner's supervisor has suggests that because the instant claims have not conformed to the narrow claim language format as described in the TC1600 memo, that the claims will be giving an interpretation that reads on any portion of the SEQ ID NOs described in claim 18. Accordingly, the applicant's claim amendments and arguments are unpersuasive.

Therefore, the examiner hereby withdraws the rejection of claim 13 under 35 U.S.C. 102(b) as being anticipated by Morris (WO2003/039484), but maintains the rejection of claims 18-20 under 35 U.S.C. 102(b) as being anticipated by Morris.

The examiner reiterates the pending rejection:

Claims 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris (WO2003/039484, published 15 May 2003). Morris teaches SEQ ID NO:16, an

isolated nucleic acid comprising a portion of instant SEQ ID NO:1 encompassing the dinucleotide "CC."

The instant claims recite "***an*** isolated nucleic acid having ***wherein the*** sequence is at least 90% identical to SEQ ID NO:1." According to Technology Center 1600 procedure the examiner is instructed to interpret this type of claim language broadly: Claim language such as claim 18 encompasses nucleic acids that comprise the full-length sequence of SEQ ID NO: 1 or any portion of SEQ ID NO: 1. This claim is anticipated by any nucleic acid comprising any dinucleotide or larger oligonucleotide which is a portion of SEQ ID NO:1.

If the claim 18 were amended to recite "An isolated nucleic acid **comprising** ~~***wherein***~~ the nucleic sequence ***having*** ~~***is***~~ at least 90% ***sequence identity*** ~~***identical***~~ to SEQ ID NO:1 or SEQ ID NO:2," the examiner would interpret the claims to encompass only nucleic acids that comprise 90% identity to the full length of SEQ ID NO: 1 (or SEQ ID NO:2), with or without additional nucleotides at either or both ends. It is also suggested that claim 19 be amended in a similar way. This claim language would overcome the pending 102 rejection based upon anticipation by Morris.

35 USC 112, 1st paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-12, and 14-17 remains rejected under 35 USC 112, 1st paragraph (written description) for the reasons of record and the comments below.

The applicant's claim amendments and arguments have been fully considered but are unpersuasive.

The applicant has argued that the written description issues regarding the pending claims resemble Example 11B from the Written Description Guidelines (March 25, 2008, Revision 1). The examiner had made comparisons of the instant claims to Example 11A. The main difference between the two Written Description Guideline Examples is that in the case of Example 11A, the activity of the polypeptide encoded by the nucleic acid was not known, while in the case of Example 11A, the activity of the polypeptide encoded by the nucleic acid was known. The applicant has essentially argued that since SEQ ID NO:1, 2 and 4 are sequences which have been demonstrated as having anti-apoptotic activity, these sequences have a known activity. Therefore, a skilled artisan would conclude that the applicant would be in possession of sequences having 90% identity to SEQ ID NO:1, 2, and 4 and which have anti-apoptotic activity, because the "core sequences" of SEQ ID NO: 1, 2, and 4 are known. Furthermore, the applicant presents arguments where portions of the specification demonstrate that the

applicant was aware of domains which are conserved in their anti-apoptotically active nucleic acid sequences.

Applicants' arguments have been fully considered but are not persuasive. In the instant case, the SEQ ID NO:1, 2, and 4 are completely synthetic and were unknown in the art at the time of filing. Upon review of homology searches, the sequences have no known homology to anti-apoptotically active molecules, or any significant homology with any known sequence. In the instant case, the three specific sequences were identified through a screening procedure. The present specification provides no guidance nor description to any rational in design or a comparison of these sequences that were identified, therefore the skilled artisan would not know what rational approach to take to make modifications with any predictable outcome on the function. It is noted that the applicant is not required to indicate how the sequences were generated. Furthermore, the applicant is not required to provide a mechanism of action of these aptamers. However, since the sequences are novel and there is no known similarity to molecules having a similar function, the art provides no basis for a link between the structure and function, and fails to provide adequate description for any modification of a sequence and maintaining it's function beyond the sequences disclosed. Therefore, it is incumbent on the applicant to provide this nexus, in order to be given credit for possession of a larger genus of molecules related to these individual species. Otherwise, the Written Description guidelines suggest that the applicant is entitled to only the species specifically recited as having this activity. The examples in the Written Description guidelines are more similar to those involving discovery of new EST or

genes encoding a novel enzyme. The applicant has suggested that known domains are conserved between the few examples of anti-apoptotically active nucleic acids provided in the specification. The applicant has stated that the "core sequence" of SEQ ID NO:1, 2, and 4 is SEQ ID NO:3 (Remarks, filed 5/19/2009, page 6, lines 24-26). In addition, the applicant has stated that over 40% of the entire sequence of SEQ ID NO:2 encompasses Helix H1, which the applicant indicates is "important to activity" (Remarks, page 7, lines 3-6). In addition, the applicant indicates that mutation in Helix F may be tolerated [and presumably retain anti-apoptotic activity] (clause inserted by examiner). Nevertheless, because of the novelty of these sequences and the lack of specific teachings linking structure to its function, the examiner concludes that the specification does not reasonably convey to a skilled artisan that the inventor has possession of the claimed subject matter at the time of filing.

Therefore, claims 1, 8-12, and 14-17 remain rejected under 35 USC 112, 1st paragraph (written description).

The examiner reiterates the pending rejection:

Claims 1, 8-12, and 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass a genus of nucleic acids having at least 80% to identity to SEQ ID NO:1-2 and having anti-apoptotic activity of at least 70%, 80%, 90%

and 95% inhibition. Under the new Written Description Guidelines (March 25, 2008, Revision 1) the examiner is directed to determine whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing. The following considerations are critical to this determination:

a. Actual Reduction to Practice. In the instant case, the specification shows two embodiments, SEQ ID NO:2 (aptamer 89) and SEQ ID NO:4 (aptamer 89-2) which are reduced to practice. Both of these sequences showed anti-apoptotic activity in assays provided in the specification (Examples 6-7, Table 2).

b. Disclosure of structure. The applicant has provided sequence listings of SEQ ID NO:1 (DNA), SEQ ID NO:2 (RNA) and SEQ ID NO:4 (RNA). SEQ ID NO:2 (66 nucleotides) and SEQ ID NO:4 (58 nucleotides) share a core structure which is 100% identical for 53 contiguous nucleotides. Additionally, with the help of a computer, a skilled artisan could identify all nucleic acids which are at least 80% identical to the full length sequence of SEQ ID NO:1 or 2. However, neither the specification nor the art indicate a relationship between the structure of the claimed genus of nucleic acids and the recited anti-apoptotic activity. In particular, there is no indication in the art or specification as to the effect of varying up to 20% of the nucleic acids of the claimed genus of isolated on the anti-apoptotic function of the nucleic acids that are not 100% identical to SEQ ID NO:1, 2, or 4.

c. Sufficient relevant identifying characteristics. As mentioned in "b" above, the complete sequence of SEQ ID NO:1, 2, and 4 are provided. Furthermore, the functional characteristics of these sequences have been demonstrated in Examples 6-7

(Spec., pages 17-18). These sequences demonstrate anti-apoptotic activity. The specification indicates, "Anti-apoptotically active, in the sense of the present invention, means that the corresponding substance in the inhibition test according to Example 6, causes an inhibition index of at least 50%, preferably at least 60%, especially preferably at least 70%, even more preferably at least 80%, even more preferably still at least 90% and most preferably of all at least 95 % in relation to the control with TSP-I-induced apoptosis." (page 6, line 28 to page 7, line 2). Because of the specification's description of assays for testing anti-apoptotic activity and the specification's narrow definition of the activity being measured in Examples 6-7, it seems that a skilled artisan would be clearly able to test a genus of polynucleotides having at least 80% identity to SEQ ID NO:1-2.

However, based on the new written description guidelines, the examiner should conclude that the applicant was not in possession of the claimed genus of isolated nucleic acids based on disclosure of the limited species of SEQ ID NO:1, 2 or 4. SEQ ID NOs: 2 and 4 were found to have anti-apoptotic activity. SEQ ID NO:2 (66 nucleotides) and SEQ ID NO:4 (58 nucleotides) share a core structure which is 100% identical for 53 nucleotides. The difference between SEQ ID NO:2 and SEQ ID NO:4 occurs in the 13 bases at the 3' end of the molecules. Therefore, the entire analysis of which portions of SEQ ID NO:2 which can be varied and maintain anti-apoptotic activity was performed on the 20% of SEQ ID NO:2 which is located in the 3' end. The breadth of the claims encompasses alterations throughout the molecule. Therefore, the examiner concludes there is limited description of the structure-function relationship

between nucleic acid molecule having at least 90% identity to SEQ ID NO:2 and their anti-apoptotic activity and the examiner further concludes a skilled artisan would find the specification inadequately describes the nucleic acids encompassed by the claimed genus.

In the instant case, the SEQ ID NO:1, 2, and 4 were unknown to the art and have no known homology to anti-apoptotically active molecules. The applicant is not required to indicate how the sequences were generated. Furthermore, the applicant is not required to provide a mechanism of action of these aptamers. Upon review of homology searches, the sequences have no known homology to anti-apoptotically active molecules, or any significant homology with any known sequence. In the instant case, the three specific sequences were identified through a screening procedure. The present specification provides no guidance nor description to any rational in design or a comparison of these sequences that were identified, therefore the skilled artisan would not know what rational approach to take to make modifications with any predictable outcome on the function. However, since the sequences are novel and there is no known similarity to molecules having a similar function, the art provides no basis for a link between the structure and function. Therefore, it is incumbent on the applicant to provide this nexus, in order to be given credit for possession of a larger genus of molecules related to these individual species. Otherwise, the Written Description guidelines suggest that the applicant is entitled to only the species specifically recited as having this activity. The examples in the Written Description guidelines which are applicable to the instant application are those involving discovery of new EST

sequences or to genes encoding a novel enzyme. The applicant has suggested that known domains are conserved between the few examples of anti-apoptotically active nucleic acids provided in the specification. The applicant has stated that the "core sequence" of SEQ ID NO:1, 2, and 4 is SEQ ID NO:3 (Remarks, filed 5/19/2009, page 6, lines 24-26). However, this is not reflected in the claims. In addition, the applicant has stated that over 40% of the entire sequence of SEQ ID NO:2 encompasses Helix H1, which the applicant indicates is "important to activity" (Remarks, page 7, lines 3-6). In addition, the applicant indicates that mutation in Helix F may be tolerated [and presumably retain anti-apoptotic activity] (clause inserted by examiner). Nevertheless, because of the novelty of these sequences and the lack of specific teachings linking the nucleic acid's structure to its function, the examiner concludes that the specification does not reasonably convey to a skilled artisan that the inventor has possession of the claimed subject matter at the time of filing.

d. The method of making the claimed invention is not well established. While a computer can generate the range of sequences encompassed by the structural limitations of the claims, a skilled artisan would not know how to modify SEQ ID NO:1, 2 and 4 to maintain the claimed function. Furthermore, the dependent claims 9-10 contains limitations about the activity level. Which modifications can accomplish this alteration if activity is not transmitted to a skilled artisan by the specification.

e-f. The level of skill in the art, and the predictability in the art are all well established and/or very predictable to a skilled artisan, with regard to generating the genus of polynucleotides having at least 90% to SEQ ID NO:1 or 2. Likewise, screening

such a genus would be easy for a skilled artisan. However, predicting which nucleotides can be varied from SEQ ID NO:1 or 2 and still retain anti-apoptotic activity would be unpredictable, based on the state of the art and the instant application.

Therefore, the examiner concludes that there is insufficient written description of the instantly claimed genus.

Allowable Subject Matter

SEQ ID NO:1, 2 and 4 are free of the art.

In addition, the Specification indicates that "the object of the present invention is to provide substances which can inhibit a TSP-1 induced apoptosis of eukaryotic cells" (page 4, lines 20-21). Accordingly, the examiner searched human Thrombospondin-1 (TSP-1) for sequences homologous to instant SEQ ID NO:1, 2, 3, and 4. The human TSP-1 mRNA does not contain any sequences homologous to SEQ ID NO:1-4. Therefore, the examiner concludes that the claimed sequences are not merely antisense nucleic acids derived from human Thrombospondin-1 sequence. This provides further evidence that the claimed sequences are not obvious.

In addition, the examiner requested an "oligo" search for SEQ ID NOs: 1, 2 and 4. There were no results from this sequence search that satisfied the limitations of claim 13.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim 13 is allowed. Claims 1, 8-10 and 14-20 are rejected.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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